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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
08/981,310	12/16/97	LANDEGREN	U	1209-121P

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EXAMINER	
PORTNER, V	
ART UNIT	**PAPER NUMBER**
1641	12

DATE MAILED: 06/08/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/981,310	Applicant(s) Landegren
	Examiner Portner	Group Art Unit 1641

☒ Responsive to communication(s) filed on *Mar 9, 1999* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-6 and 8-10* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-6 and 8-10* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *9*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claims 1-6 and 8-10 are pending.

Information Disclosure Statement

1. The information disclosure statement filed October 20, 1998 has been considered as to the merits prior to this action.

Sequence Letter

2. Applicant has made a bonafide attempt to provide a computer readable form to the Patent and Trademark Office but the sequence disc contained errors which could not be corrected by the Office. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821 (a) (1) and (a) (2) (SEE page 7, paragraph 3 and 4). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.136. In no case may and applicant extend the period of response beyond the six month statutory period. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.

3. In the Amendment submitted on March 9, 1999, the paper copy of the sequence listing provided was directed to be inserted after the abstract of the Specification. The examiner believes that the Sequence listing is to be inserted just prior to the claims. Direction to insert the sequence listing to the appropriate location is requested.

Rejections Maintained

Claim Rejections - 35 U.S.C. § 112

4. Claims 6 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6 in section e) recites the phrase "amplifying said cross linked oligonucleotide" as the claim does not recite a cross linking step it is not clear when or how the "crosslinkable oligonucleotide" became cross linked. Claim 6 has been amended to recite the phrase in section c) "become cross linked" but at which point or by what means the cross linking takes place is still not clearly set forth. From the claim language recited, the second and third antibodies upon binding epitopes on the same antigen *instantaneously* "become cross linked". If this is the case, the component which results in cross linking is not defined in the claims. Amplification of cross linked oligonucleotide which do not evidence any free ends, specifically a 5' phosphate, and a 3' hydroxyl group ligation would not take place and amplification would also not take place with out a starting point with free ends. From the specification, the oligonucleotide disclosed are SEQ ID

NO 1-4, it is not clearly apparent what portions of the oligos are complementary to each other in order to provide for an amplified product without the addition of primers to the immunoassay.

5. The use of the word "crosslinkable" or "cross linked" implies both a non-specific and specific cross linking events. A non-specific cross linking event such as through the use of glutaraldehyde or other known cross linking reagent would result in a covalent relationship between the oligonucleotide. If a non- specific cross linking process is carried out, then the reagent needed for this process should be set forth in such a way as to provide clarity to how the oligonucleotide once cross linked could also be amplified. If a specific cross linking event which produces cross linked oligonucleotide, the recitation of the term "ligated" or "ligatable" or the defining of the specific reagent which carrier out the specific cross linking event would provide greater clarity to the claim.

6. In claim 6, sections b) and d) provide for washing off excess reagents, but what is contained in the reagents other than the first, second and/or third antibodies is not clearly defined in the claims. The word "reagents" lacks antecedent basis in the claim. In the case of section b), the excess reagents is excess *sample*, as only a sample is applied to the immobilized antibody of section a). The immobilized antibody would not be removed with a washing step. Amendment of section b) of claim 6 to recite "washing off excess" --sample-- could obviated a portion of this rejection. Section d) of claim 6, if amended to recite the phrase "washing off excess" --solution-- could obviate a portion of this rejection.

7.

Claim Rejections - 35 U.S.C. § 103

8. Claims 1-5 remain rejected under 35 U.S.C. 102(e) as being anticipated by or in the alternative as being obvious over Urdea (US Pat. 5,656,731).

9. Claims 1, 3-5 remain rejected under 35 U.S.C. 102(e) as being anticipated by or in the alternative as being obvious over Birkenmeyer et al (US Pat. 5,667,974).

10. Claims 1, 3-5 are rejected under 35 U.S.C. 103(a) as being obvious over Nickerson et al (1992) or Delahunty et al (1995) or Kwok et al (1992) or Nilsson et al (1994)

11. Claims 1-2 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al taken with Dattagupta et al (US Pat. 4,~~78~~746,111).

12. Claims 3-5 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (US Pat. 5,026,653) taken with Dattagupta as applied to claims 1-2 and 6 above and further in view of Ciechanover et al (US Pat. 5,384,255).

Response to Arguments

13. **Urdea** et al is argued to not disclose the instantly claimed method of signal production and therefore does not anticipate or obviate the instantly claimed invention.

14. Applicant's arguments filed with respect to Urdea et al have been fully considered but they are not persuasive because the reagents contained in the kits of claims 1-5 may be used in any assay method or for any purpose and are not limited to the claimed immunoassay. Claim 1 has been amended to recite functional language which states "wherein a signal is generated when said

second and third affinity reagents are bound to the same macromolecule", but not signal component is in association with the antibodies, no labels are bound to the antibodies, the type of signal produced is not defined in the claims. This functional limitation does not add clarity to the signal which Applicants argues as the point of novelty of the instantly claimed invention because how the signal is produced or by what the signal is produced or how the signal can be determined is not clear. The antibodies only need to bind to the same macromolecule and a signal is produced. It is not clear that the nature of the macromolecule is inherently fluorescent and the binding of the antibodies enhances or reduces the native fluorescence contained therein sufficiently to determine that the antibodies have bound. The recitation of a signal being generated does not patentably distinguish over the applied prior art. Urdea et al was not applied to the immunoassay method claims but only to the product kits claims. Therefore, claims 1-5 remain rejected for reasons of record on paper number 7.

15. **Birkenmeyer** et al is argued to only disclose a kit for the detecting nucleic acids and not a general kit, nor is the disclosure of Birkenmeyer require that the assay components function in such a way that "simultaneous recognition of two or more determinants" in order to amplify the signal.

16. Applicant's arguments filed with respect to Birkenmeyer et al have been fully considered but they are not persuasive because the reagents contained in the kits of claims 1, 3-5 may be used in any assay method or for any purpose and are not limited to the claimed assay method. Claim 1

has been amended to recite functional language which states "wherein a signal is generated when said second and third affinity reagents are bound to the same macromolecule", but no signal component is in association with the antibodies, no detectable labels are bound to the antibodies, the type of signal produced is not defined in the claims. This functional limitation does not add clarity to the signal which Applicants argues as the point of novelty of the instantly claimed invention because how the signal is produced or how it is determined, as well as by what the signal is produced is not clear. The antibodies only need to bind to the same macromolecule and a signal is produced. It is not clear that the nature of the macromolecule is inherently fluorescent and the binding of the antibodies enhances or reduces the native fluorescence contained therein sufficiently to determine that the antibodies have bound. The recitation of a signal being generated does not patentably distinguish over the applied prior art. Birkenmeyer et al was not applied to the method claims but only to the product kits claims which may comprise any first, second and third affinity reagents, to include nucleic acids. Therefore, claims 1, 3-5 remain rejected for reasons of record on paper number 7.

17. **Nickerson et al , Delahunty et al , Kwok et al and Nilsson et al (1994)** are argued to be drawn to a different inventive concept and that there is "no suggestion in Nickerson et al, Delahunty et al., Kwok et al or Nilsson et al of detecting macromolecules such as protein antigens.

18. Applicant's arguments filed with respect to Nickerson et al (1992) or Delahunty et al (1995) or Kwok et al (1992) or Nilsson et al (1994) have been fully considered but they are not

persuasive because the statement of intended use does not patentably distinguish over the prior art, wherein the kits are products which may be used for may purpose and in any method, and the affinity reagent is not limited to the determination of proteins but may be any affinity reagent to include lectins, receptors, single chain antibodies, cofactors or nucleic acids. Therefore the claims kits are not limited to antibodies for the determination of protein antigens, but are kits for the determination of any analyte which evidences multiple binding sites to which first, second and third affinity reagents may bind. Therefore, claims 1, 3-5 remain rejected for reasons of record on paper number 7.

19. **Lee in view of Dattagupta** is argued to disclose assay methods which utilize two antibodies in a standard sandwich immunoassay format and Dattagupta et al "merely teach the conjugation of oligonucleotide to a protein" and do not suggest improving assay sensitivity by requiring the simultaneous binding of at least two probes to create a signal.

20. Applicant's arguments filed with respect to Lee in view of Dattagupta have been fully considered but they are not persuasive because Applicant focused on only one embodiment disclosed by Lee and Lee et al does disclose a three site or more immunoassay based on antigens having three or multiple separate and distinct epitope binding sites, wherein two antibodies are in the soluble phase and are detectably labeled and at least one antibody is immobilized on the solid phase (Lee, col. 5, lines 1-68). Lee teaches that the use of multiple affinity reagents can: "increase the sensitivity of antigen binding assays", "eliminate the cross reactivity of antigen analogs", "eliminate the interference of circulating antibodies in human serum sample" and "eliminate

interference from analogs of the antigen" (Lee, col. 6, lines 53-64). Therefore, contrary to Applicant's assertion that Lee do not suggest that this type of immunoassay format provides for increase assay sensitivity, Lee clearly teaches four advantages, to include increased assay sensitivity, for the use of multiple antibodies for the specific binding of multiple separate and distinct epitopes for the detecting the presence of a specific antigen. With respect to the assertion that Dattagupta et al "merely teach the conjugation of oligonucleotide to a protein", it is the position of the examiner that Dattagupta teaches far more than mere conjugation of a nucleic acid to a protein. Dattagupta teaches the conjugation of a nucleic acid to IgG (col. 3, lines 56-61) and the use of the covalently coupled IgG-nucleic acid reagent in immunoassay formats. The labeled reagent of Dattagupta is taught to provide an improvement over the prior art wherein the immunoassay is highly sensitive (col. 2, lines 51-58), and convenient. Applicant's argument that the prior art does not "suggest improving assay sensitivity by requiring the simultaneous binding of at least two probes to create a signal" is not commensurate in scope with the instantly claimed invention of claim 6, wherein no "probes" are recited in claim 6, the binding is not required to be simultaneous and the phrase "at least two" does not appear in the claim. The prior art does suggest the an improved highly sensitive immunoassay, wherein Lee teaches the use of three distinct and separate epitopes in an immunoassay to achieve increased sensitivity and Dattagupta teaches that the use of a covalently linked IgG to a nucleic acid label provides for increased sensitivity and amplification of for the antigen antibody complex for detection is taught through the addition of a secondary reagent which increases, amplifies the detectable label (col. 4,

lines 47-61). Therefore, claims 1-2 and 6 remain rejected for reasons of record on paper number 7.

21. Lee in view of Dattagupta and further in view of Ciechanover et al is argued to "fail to disclose the simultaneous binding of two or more probes to generate a signal and thus improve the sensitivity of the assay.

22. Applicant's arguments filed with respect to Lee, Dattagupta and Ciechanover have been fully considered but they are not persuasive because (see discussion of Lee in view of Dattagupta above) the instantly claimed invention does not recite the use of two or more probes to generate a signal. Therefore, Applicant's arguments are not commensurate in scope with the instantly claimed invention. Even if the claims were amended to recite the argued limitation, Ciechanover clearly teaches the use of ligase chain reaction for the amplification of two or more oligonucleotide which are ligated in the presence of a nucleic acid target which is then amplified (col. 19, lines 46-68). This section of the disclosure of Ciechanover is drawn to antibodies detectably labeled with a DNA and further discloses different art recognized means for the amplification of a oligonucleotide for increased ease of determining the presence of a single copy of DNA. The reference clearly defines means and methods for increasing immunoassay sensitivity. Therefore, claims 2-5 and 7-8 remain rejected for reasons of record on paper number 7.

New Grounds of Rejection

Claim Objections

23. Claim 9 is objected to because of the following informalities: the word "aid" is recited on line one of the claim. It appears that this word should be --said--. Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 112

24. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
>
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

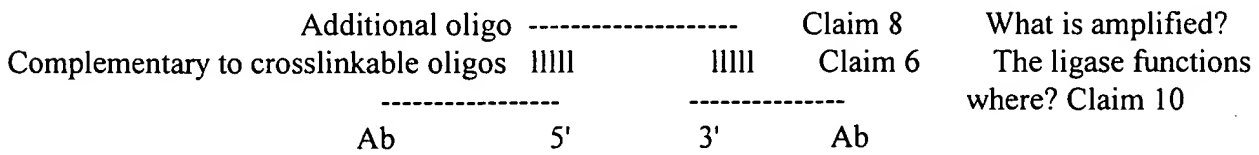
25. Claims 6, 8-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 6, in section c) recites the phrase "said, same antigen". This word "same" lacks antecedent basis in the claim. This rejection could be obviated by the deletion of the word "same" or providing antecedent basis for the recitation of this word.

b. Claim 6, in section e) recites the phrase "said cross linked oligonucleotide". The antibodies of section c) become cross linked. No wherein the claim are there recited specific

reagents for the cross linking of the oligonucleotide. Section c) does recite that the oligonucleotide are crosslinkable but within the same section of the claim, the antibodies become cross linked. Clarification of what is actually being cross linked or ligated is requested.

c. Claim 8-10 recites the method further comprises the addition of a "complementary oligonucleotide to the crosslinkable oligonucleotide before step d)". The presence of this reagent in any of steps a) or b) or c) or is added after the antibodies become cross linked and before the washing step. It is not clear to what extent the additional reagent is complementary to oligonucleotide which are bound to the second and third antibodies. It is also not clear whether the additional oligonucleotide participates in the cross linking of the antibodies of section c). If the additional complementary oligonucleotide participates in the cross linking of the oligonucleotide on the second and third antibodies this process step is not clearly defined. The type of cross linking being carried out is not clearly defined, ie. ligation, glutaraldehyde cross linking, ethanol fixation. As the additional oligonucleotide is complementary to both of the oligonucleotide of the second and third antibodies, the recitation of adding ligase in claim 10, which depends from claim 8 introduces confusion, wherein ligation must take place between a 5' Phosphate and a 3' hydroxyl group but the complimentary oligonucleotide would not be expected to be in a conformation which would permit ligation of the three oligonucleotide to one another. Where the ligase acts is not clearly defined in the claim. Figure 1, clearly shows the use of ligase to join two oligonucleotide but they are not complementary to one another, if the crosslinkable oligonucleotide are complementary to one another (claim 9), what role the ligase (claim 10) plays is unclear, as ligase joins 5' and 3' components. Clarification is requested.



Claim 9: Comp. Oligo 3'----------Ab The ligase functions
lllllllllllllllllllll where? Claim 10, What is amplified? Claim 6,
Ab ----------5' What is cross linked ?

d. The claim limitation "adding a ligase before step d)" is recited in claims 8 and 10 and would be clearer if this phrase were amended to recited ---during step c) to ligate the oligonucleotide of the second and third antibodies---- or an equivalent phrase.

e. The specification at page 7, teaches the use of complementary oligonucleotide, but the sequences disclosed are not complementary one to another. The recitation of the word complementary in the claims is not clearly defined in the specification and therefore is vague and indefinite when recited in the claims. A showing how the disclosed sequences are complementary one to another would provide clarity to the definition of this term used in the claims.

f. Claims 6, 8-10 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. The recitation and use of primers to obtain an amplified product is critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). On page 7 of the specification, the use of two primers is clearly taught as essential to the attainment of an amplified product in the method of detecting an antigen.

Claim Rejections - 35 U.S.C. § 103

g. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

h. Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hendrickson et al (reference submitted on Applicant's IDS).

Hendrickson et al (1995) disclose the use of commercially available reagents for conducting a highly sensitive multianalyte immunoassay using covalently labeled antibodies and polymerase chain reaction, wherein three different analytes were determined with a single immunoassay method which utilized immobilized reagents in the determination process . Hendrickson et al differs from the instantly claimed invention by failing to show the compilation of the reagents into kit form.

Therefore, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the disclosure of Hendrickson et al to compile the disclosed reagents into kit form because Hendrickson et al teach that the disclosed immunoassays which utilize amplifiable DNA labels provide for increased sensitivity, means of detecting a variety of analtyes, cost containment, the performance of groups or panels of tests for accurate clinical assessment and for the screening multiple agents, wherein the compilation of reagents is an art recognized means for ready availability of assay reagents which are standardized and provide ease of commercial distribution.

Conclusion

26. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

27. Richards et al (US Pat. 5,876,976) is cited to show a method for reducing carryover contamination in an amplification procedure.

28. Cantor et al (US Pat. 5,849,878) is cited to show the use of bispecific reagents, specifically DNAs as chemically and spatially defined cross linkers.

29. Carrino et al (US Pat. 5,814,492) is cited to show the use of probe making for the reduction of background in an amplification reaction.

30. Brenner (US Pat. 5,780,231) is cited to show DNA extension and analysis with rolling primers.

31.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (703)308-7543. The examiner

Conclusion

This is a non-final Office Action.

No claims are allowed.

26. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

27. Richards et al (US Pat. 5,876,976) is cited to show a method for reducing carryover contamination in an amplification procedure.

28. Cantor et al (US Pat. 5,849,878) is cited to show the use of bispecific reagents, specifically DNAs as chemically and spatially defined cross linkers.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (703)308-7543. The examiner

can normally be reached on Monday through Friday from 7:30 AM to 5:00 PM except for the first Friday of each two week period.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (703) 308-4027. The fax phone number for this group is (703) 308-4242.

The Group and/or Art Unit location of your application in the PTO will be changing February 7, 1998. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vgp
May 27, 1999

James C. Housel 6/7/99

JAMES C. HOUSEL
SUPERVISORY PATENT EXAMINER

Application No. 08/981,310

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 CFR 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 CFR 1.821 - 1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 CFR 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 CFR 1.821(e).

☒ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 CFR 1.822 and/or 1.823, as indicated on the attached copy of the marked-up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A substitute computer readable form must be submitted as required by 37 CFR 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 CFR 1.821(e).

☐ 7.

Other: _____

Applicant must provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing"

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d)

For questions regarding compliance with these requirements, please contact:

For Rules Interpretation, call (703) 308-1123
For CRF submission help, call (703) 308-4212
For PatentIn software help, call (703) 557-0400

Please return a copy of this notice with your response.